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(21) International Application Number: PCT/US93/01565 (22) International Filing Date: 22 February 1993 (22.02.93) (30) Priority data: 07/844,269 2 March 1992 (02.03.92) US (71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US). (72) Inventors: ALLI, Yusuf ; 6904 Wick Trail, Fort Worth, TX 76133 (US). BHAGAT, Haresh, G. ; 6821 Windcrest Lane, Fort Worth, TX 76133 (US). (74) Agents: CHENG, Julie et al.; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: COMBINATIONS OF CELLULOSIC POLYMERS AND CARBOXY VINYL POLYMERS AND THEIR USE IN PHARMACEUTICAL COMPOSITIONS (57) Abstract Combinations of at least one cellulosic polymer and at least one carboxy vinyl polymer have an unexpectedly high viscosity. Compositions containing these polymeric combinations have a number of applications, such as in pharmaceuticals, especially in the field of ophthalmics. Topical ophthalmic compositions containing these polymeric combinations are contemplated for the relief of the symptoms of dry eye syndrome.		

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COMBINATIONS OF CELLULOSIC POLYMERS AND CARBOXY VINYL POLYMERS AND THEIR USE IN PHARMACEUTICAL COMPOSITIONS

Background of the Invention

5 The present invention relates generally to viscosity building agents (viscosity enhancers). More specifically, the present invention relates to combinations of viscosity enhancers which are useful in pharmaceutical compositions, especially in ophthalmic pharmaceuticals and artificial tear formulations. The compositions of the present invention are also useful as lubricating and cushioning agents for the eye after traumatic injury or surgery.

10 Carboxy vinyl polymers have been used since the 1950's as viscosity enhancers in a number of fields, including cosmetics and pharmaceuticals. See, for example, Chemical & Engineering News, September 29, 1958, pages 64-65. Cellulosic polymers are also known in the pharmaceutical arts to be viscosity building agents.

15 US 4,039,662 (Hecht et al.) discloses the use of cellulosic polymers in ophthalmic solutions suitable as artificial tears; however, the ophthalmic solutions of Hecht et al. additionally require a polysaccharide and benzalkonium chloride. Further, addition of cellulosic polymers to such solutions do not greatly increase the viscosity. For example, the ophthalmic solutions of Hecht et al. have a viscosity between about 1 and about 25 centipoise (cps).

20 US 5,075,104 (Gressel et al.) and related U.S. Patent Application Serial No. 07/716,426 filed June 17, 1991 (Gressel et al.) disclose the topical use of compositions containing carboxy vinyl polymers for the relief of the symptoms of dry eye syndrome. There is no discussion in either Gressel et al. references relative to the use of cellulosic polymers.

Summary of the Invention

Viscosity is generally dependent upon molecular weight and concentration. The present invention is based on the unexpected finding that compositions comprising certain combinations of at least one cellulosic polymer and at least one carboxy vinyl polymer are much more viscous than similar compositions containing only one type of polymer. That is, a lower polymer concentration is required to achieve a higher viscosity when polymer combinations of the present invention are utilized than when only one of the polymers is utilized. This is particularly beneficial in the ophthalmic field, since a reduction in the overall polymer concentration in an ophthalmic composition generally results in patient greater comfort. On the other hand, using the polymer combinations of the present invention, higher viscosity can be achieved without increasing the overall polymer concentration. This aids in retention of the composition in the eye and permits the maintenance of a longer moisturizing effect, of particular importance with respect to artificial tear formulations.

Brief Description of the Drawing

Figure 1 is a graph comparing the viscosities of Formulations B (0.5% HPMC), F (0.175% Carbomer 934P) and L (0.5% HPMC + 0.175% Carbomer 934P) of Example 1.

Detailed Description of the Invention

Combinations of at least one cellulosic polymer with at least one carboxy vinyl polymer have unexpectedly been found to provide potentiation of viscosity. The compositions of the present invention comprise such polymer combinations and have many potential applications, particularly in the field of pharmaceuticals. The

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compositions of the present invention are especially useful for the treatment of dry eye syndrome and related ailments.

The cellulosic polymers useful in the pharmaceutical compositions of the present invention include all cellulose derivatives which exhibit viscoelastic properties. In general, such cellulosic polymers have an average molecular weight between about 10,000 and 13 million. Preferred cellulosic polymers include: hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) and methyl cellulose (MC). In general, these cellulosic polymers are present in the compositions of the present invention at a concentration between about 0.05 and about 5.0 percent by weight (wt%), preferably between about 0.25 and about 1.0 wt%. It is especially preferred to use the cellulosic polymers at a concentration of about 0.5 wt%.

The carboxy vinyl polymers useful in the pharmaceutical compositions of the present invention have an average molecular weight between about 500,000 and 6 million. The polymers are characterized as having carboxylic acid functional groups and preferably contain between 2 and 7 carbon atoms per functional group. Suitable carboxy vinyl polymers include those called carbomers, e.g., Carbopol® (B.F. Goodrich Co., Cleveland, Ohio). Specifically preferred are: carbomer 910, carbomer 940, carbomer 934P and carbomer 1342. (Carbomer 934P is the most preferred.) Such polymers will typically be employed in an amount between about 0.05 and about 3.0 wt%, depending on the desired viscosity of the composition. It is preferred to use the carboxy vinyl polymers at a concentration between about 0.1 and about 0.5 wt%, most preferably at a concentration of about 0.175 wt%.

The wt% ratio between cellulosic polymer and carboxy vinyl polymer is generally between about 1:60 and about 1:0.025, preferably between 1:0.4 and about 1:0.3.

The compositions of the present invention may also contain one or more pharmaceutically active agents ("actives"). Such actives include, but are not limited to: glaucoma agents, such as miotics (e.g., pilocarpine, carbachol and acetylcholinesterase inhibitors), sympathomimetics (e.g., epinephrine, dipivalylepinephrine and para-amino clonidine), beta-blockers (e.g., betaxolol, levobunolol and timolol) and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide); dopaminergic antagonists; antihypertensive agents, such as para-amino clonidine (also known as apraclonidine); anti-infectives, such as ciprofloxacin; non-steroidal and steroidal anti-inflammatories, such as suprofen, ketorolac, tetrahydrocortisol, dexamethasone and rimexolone; prostaglandins; retinoids; aldose reductase inhibitors; proteins; growth factors, such as epidermal growth factor; and anti-allergics.

Compositions of the present invention which are suitable for the treatment of dry eye syndrome and other related ailments may also include the following actives: zinc sulfate, Dextran 70, gelatin, glycerin, polyethylene glycols, polysorbates, polyvinyl alcohols and polyvinylpyrrolidone (Povidone). These actives, when present, are generally utilized in the compositions of the present invention at a concentration between about 0.005 to about 2.5 wt%.

The compositions of the present invention may additionally contain various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. The final composition pH may also be adjusted so that it is in the physiological range (between about 5 and about 8.5), such as by the addition of sodium hydroxide and/or hydrochloric acid. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1 (Polyquad®) and other agents equally well-known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.0001 to 1.0 wt%. Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include: sodium chloride, potassium chloride, mannitol, dextrose, sucrose, glycerin and propylene glycol. Such agents, if utilized, will typically be

employed in an amount between about 0.5 to 6 wt% and the osmolality will typically be between about 200 and 360 milliOsmoles/kilogram (mOsm/kg), preferably between about 250 and 340 mOsm/kg.

The compositions of the present invention generally have a viscosity between about 50 and about 15,000 cps, preferably between about 2,000 and about 10,000 cps, and most preferably between about 3,000 and about 6,000 cps. The viscosity of such compositions will vary, depending on the particular polymer combinations used and the relative concentrations of each polymer.

The compositions of the present invention are typically formulated by dissolving the tonicity agent in purified water, followed by addition of an antimicrobial preservative agent if desirable. The polymers, previously dissolved in purified water, are then added and the final volume obtained by the addition of purified water. The batch is adjusted for a desirable pH by using sodium hydroxide and/or hydrochloric acid. The bulk product is then subjected to steam sterilization and packaged in either single dose or multiple dose containers according to methods known in the art. If such compositions contain one or more actives, the active is generally incorporated into the compositions prior to addition of the polymers.

The following examples are presented to illustrate further various features and certain preferred embodiments of the present invention and should not be interpreted to limit the scope of the invention in any way.

EXAMPLE I

Table I, below, illustrates some samples which were prepared for the purpose of comparing viscosity. The samples were prepared by dissolving the cellulosic polymer and/or carboxy vinyl polymer in purified water followed by adjustment of pH using sodium hydroxide and/or hydrochloric acid. Sample size was adjusted to final volume and subjected to steam sterilization.

TABLE I

SAMPLE	INGREDIENTS				
	Hydroxypropyl methyl cellulose (2910)	Hydroxymethyl cellulose (2208) (K100M)	Hydroxyethyl cellulose	Carbomer 934P	Purified Water
A	0.25	---	---	---	QS 100
B	0.5	---	---	---	QS 100
C	---	0.25	---	---	QS 100
D	---	0.5	---	---	QS 100
E	---	---	0.5	---	QS 100
F	---	---	---	0.175	QS 100
G	---	---	---	0.175	QS 100
H	0.20	---	---	0.175	QS 100
J	0.3	---	---	0.175	QS 100
K	0.4	---	---	0.175	QS 100
L	0.5	---	---	0.175	QS 100
M	0.5	---	---	0.15	QS 100
N	0.5	---	---	0.2	QS 100
O	---	0.25	---	0.175	QS 100
P	---	0.5	---	0.175	QS 100
Q	---	---	0.5	0.175	QS 100

After cooling to room temperature, the viscosities of Samples F through Q were measured using a Brookfield RVT viscometer equipped with a CP-51 cup for a room temperature (25°C) sample at 2-5 RPM (revolutions per minute). For the less viscous samples (Samples A through E), the Brookfield LVT viscometer was equipped with a CP-42 cup at 3 RPM (25°C). Table II, below, presents the viscosities of the different Samples. In addition, Figure 1 graphically illustrates the differences in viscosity between Samples B (0.5% HPMC), F (0.175% carbomer 934P) and L (0.5% HPMC and 0.175% carbomer 934P).

TABLE II

	A	B	C	D	E	F	G	H	J	K	L	M	N	O	P	Q
Viscosity (cps)	4	3	22	57	29	1330/ 1460	1970	1435	2255	3360	4860	3180	6830	2770	3813/ 4900	2400/ 2500

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As best seen in Figure 1, 0.5% hydroxypropyl methyl cellulose (Sample B) generates a viscosity of only 4 cps. Likewise, 0.175% carbomer 934P alone (Sample F) has a viscosity between 1330 - 1460 cps. On the other hand, when these components are combined (Sample L) the viscosity is 4860 cps. This clearly indicates the potentiation of viscosity.

EXAMPLE II

The following Table III represents some preferred embodiments of compositions of the present invention. Formulations 1 and 2 are the most preferred and their preparation procedures are detailed below. Preparation of the other formulations are analogous to the procedures of Formulation 1 (with preservative) or Formulation 2 (preservative-free).

TABLE III

FORMULATIONS	INGREDIENTS*					
	HPMC (2910)	Carbomer 934P	HEC	Mannitol	Benzalkonium Chloride	Purified Water
1	0.5	0.175	---	4.5	0.008	QS 100
2	0.5	0.175	---	5.0	---	QS 100
3	0.5	0.2	---	5.0	0.008	QS 100
4	0.5	0.2	---	4.5	---	QS 100
5	0.5	0.15	---	4.5	0.008	QS 100
6	0.5	0.15	---	5.0	---	QS 100
7	0.20	0.175	---	5.075	0.008	QS 100
8	0.20	0.175	---	4.50	---	QS 100
9	---	0.175	0.75	5.0	0.008	QS 100
10	---	0.175	0.75	4.5	---	QS 100
11	---	0.175	0.5	5.0	0.008	QS 100
12	---	0.175	0.5	4.5	---	QS 100
13	---	0.175	1.0	5.0	0.008	QS 100
14	---	0.175	1.0	4.5	---	QS 100

*NaOH and/or HCl also may be added for pH adjustment.

Preparation of Formulation 1 (Preservative-free):

Mannitol was mixed with 60% of the total water volume until dissolved (about 2 minutes), then Carbomer 934P was slowly added and the mixture stirred until the slurry was uniform and had no visible lumps. The pH was adjusted to 7.3-7.5. A
5 second mixture was made by dispersing the HPMC into hot (65-90°C) purified water (approximately 25% of the total water volume). The two mixtures were combined, mixed for about 15 minutes (min) and the pH adjusted if necessary. Purified water was then added to bring the total volume to 100% and the mixture stirred to obtain homogeneity (a minimum of 10 min).

10 Sterilization and packaging were accomplished by methods known to those skilled in the art.

Preparation of Formulation 2 (with Preservative):

Formulation 2 was prepared according to the procedure of Formulation 1, except that benzalkonium chloride (10% solution in water) was added before the first
15 pH adjustment (after the addition of mannitol and carbomer 934P, but before the addition of HPMC).

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential
20 characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. A viscous ophthalmic composition comprising a combination of:
between about 0.05 and about 5.0 percent by weight of a cellulosic polymer having an
average molecular weight between about 10,000 and about 13 million; and between
5 about 0.05 and about 3.0 percent by weight of a carboxy vinyl polymer having an
average molecular weight between about 500,000 and about 6 million.

2. The composition of claim 1, wherein the composition has a viscosity
between about 50 and about 15,000 centipoise.

3. The composition of claim 2, wherein the composition has a viscosity
10 between about 2,000 and about 10,000 centipoise.

4. The composition of claim 3, wherein the composition has a viscosity
between about 3,000 and about 6,000 centipoise.

5. The composition of claim 1, wherein the cellulosic polymer is selected
from the group consisting of: hydroxypropyl methyl cellulose, hydroxyethyl cellulose,
15 hydroxypropyl cellulose and methyl cellulose.

6. The composition of claim 1, wherein the cellulosic polymer is present at
a concentration between about 0.25 and about 1.0 percent by weight.

7. The composition of claim 6, wherein the cellulosic polymer is present at
a concentration of about 0.5 percent by weight.

8. The composition of claim 6, wherein the cellulosic polymer is present at
20 a concentration of about 0.25 percent by weight.

9. The composition of claim 1, wherein the carboxy vinyl polymer is selected from the group consisting of: carbomer 910, carbomer 940, carbomer 934P and carbomer 1342.

10. The composition of claim 9, wherein the carboxy vinyl polymer
5 comprises carbomer 934P.

11. The composition of claim 1, wherein the carboxy vinyl polymer is present at a concentration between about 0.1 and about 0.3 percent by weight.

12. The composition of claim 11, wherein the carboxy vinyl polymer is present at a concentration of about 0.15 percent by weight.

10 13. The composition of claim 11, wherein the carboxy vinyl polymer is present at a concentration of about 0.175 percent by weight.

14. The composition of claim 11, wherein the carboxy vinyl polymer is present at a concentration of about 0.2 percent by weight.

15 15. The composition of claim 1, wherein the weight percent ratio of cellulosic polymer to carboxy vinyl polymer is between about 1:60 and about 1:0.025.

16. The composition of claim 15, wherein the weight percent ratio of cellulosic polymer to carboxy vinyl polymer is between about 1:0.4 and about 1:0.3.

17. The composition of claim 1, further comprising at least one pharmaceutically active agent selected from the group consisting of: miotics,
20 sympathomimetics, beta-blockers, carbonic anhydrase inhibitors, dopaminergic antagonists, antihypertensive agents, anti-infectives, non-steroidal and steroidal anti-inflammatories, prostaglandins, retinoids, aldose reductase inhibitors and anti-allergics.

18. The composition of claim 17, wherein the pharmaceutically active agents are selected from the group consisting of: pilocarpine, carbachol, acetylcholinesterase inhibitors, epinephrine, dipivalylepinephrine, para-amino clonidine, betaxolol, levobunolol, timolol, acetazolamide, methazolamide, ethoxzolamide, ciprofloxacin, suprofen, ketorolac, tetrahydrocortisol, dexamethasone and rimexolone.

19. An aqueous ophthalmic composition useful in the treatment of dry eye syndrome and related ailments, comprising a combination of hydroxypropyl methyl cellulose at a concentration of about 0.5 percent by weight and carbomer 934P at a concentration of about 0.175 percent by weight.

20. The composition of claim 19, further comprising at least one pharmaceutically active agent selected from the group consisting of: zinc sulfate, Dextran 70, gelatin, glycerin, polyethylene glycols, polysorbates, polyvinyl alcohols and polyvinylpyrrolidone.

21. A method for the treatment of dry eye syndrome, comprising topically administering an aqueous ophthalmic composition to an affected eye, said composition comprising: between about 0.25 and about 0.75 percent by weight of a cellulosic polymer having an average molecular weight between about 10,000 and about 13 million; and between about 0.1 and about 0.3 percent by weight of a carboxy vinyl polymer having an average molecular weight between about 500,000 and about 6 million, wherein the composition has a viscosity between about 50 and about 15,000 centipoise and wherein the weight percent ratio of the cellulosic polymer to carboxy vinyl polymer is between about 1:60 and about 1:0.025.

22. The method of claim 21, wherein the aqueous ophthalmic composition further comprises at least one pharmaceutically active agent selected from the group consisting of: zinc sulfate, Dextran 70, gelatin, glycerin, polyethylene glycols, polysorbates, polyvinyl alcohols and polyvinylpyrrolidone.

23. The method of claim 21, wherein the composition has a viscosity between about 3,000 and about 6,000 centipoise.

24. The method of claim 21, wherein the cellulosic polymer is selected from the group consisting of: hydroxypropyl methyl cellulose, hydroxyethyl cellulose,
5 hydroxy propyl cellulose and methyl cellulose.

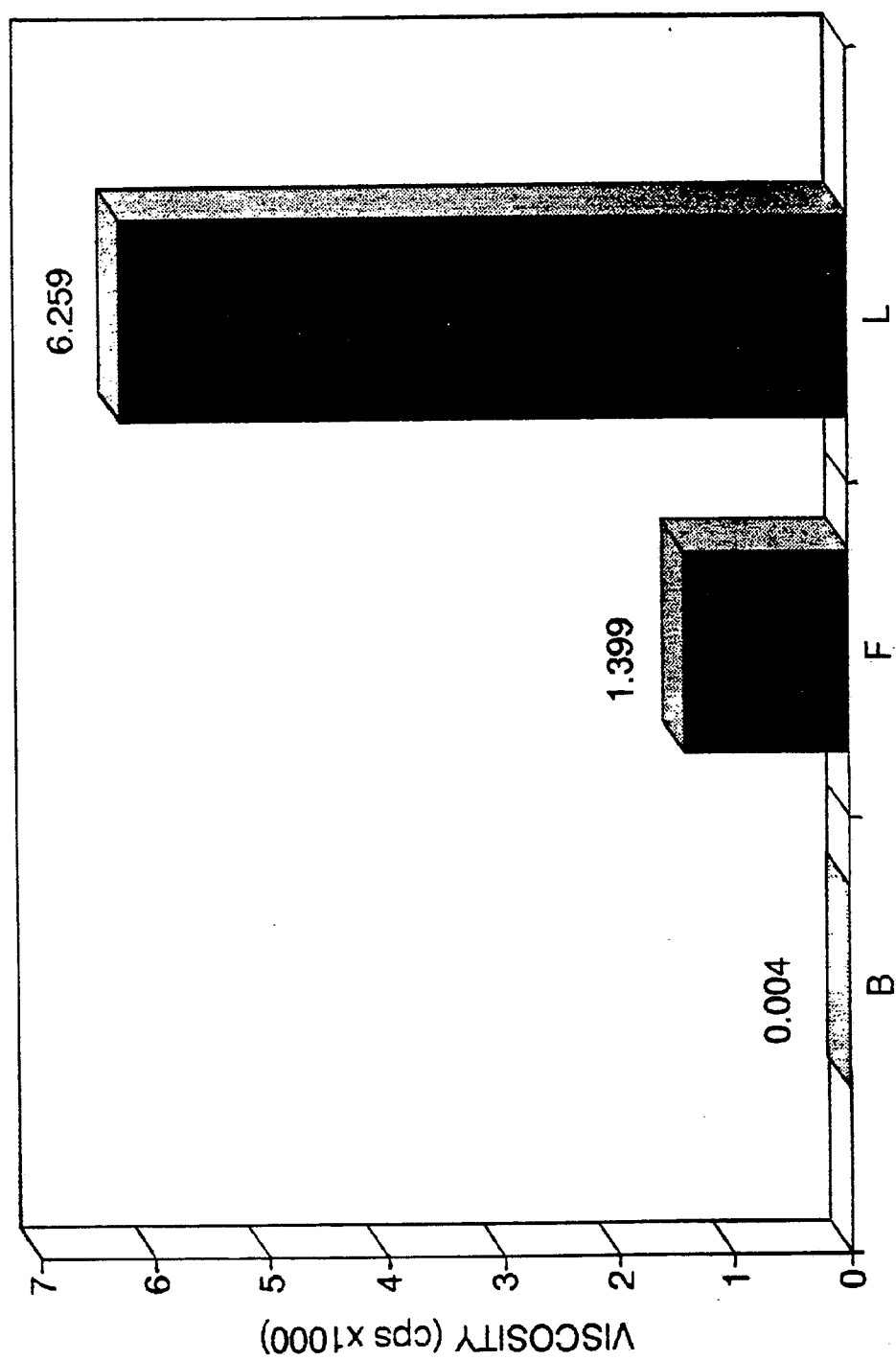
25. The method of claim 21, wherein the carboxy vinyl polymer is selected from the group consisting of: carbomer 910, carbomer 940, carbomer 934P and carbomer 1342.

26. The method of claim 21, wherein the cellulosic polymer comprises
10 hydroxypropyl methyl cellulose and the carboxy vinyl polymer comprises carbomer 934P.

27. The method of claim 21, wherein the cellulosic polymer is present at a concentration of about 0.5 percent by weight and the carboxy vinyl polymer is present at a concentration of about 0.175 percent by weight.

28. The method of claim 21, wherein the cellulosic polymer is present at a
15 concentration of about 0.5 percent by weight and the carboxy vinyl polymer is present at a concentration of about 0.175 percent by weight.

FIG. 1



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/01565

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K9/08; A61K47/38; A61K47/32		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO,A,9 119 481 (ALLERGAN INC) 26 December 1991 see page 4, line 22 - line 37 see page 5, line 4 - line 6 see page 9, line 8 - line 9 see page 10, line 8 - line 11 see page 9, line 9 see page 10, line 9 see examples see page 14, line 31 - page 16, line 23 ---	1-3, 5-7, 9, 11, 14, 16-18, 20-22, 24-26
A	US,A,3 920 810 (RANKIN B.F.) 18 November 1975 see column 1 - column 3 ---	1-20
-/--		
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
21 JUNE 1993	01.07.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	BOULOIS D.	

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	DE,A,3 440 352 (DR. THILO & CO GMBH) 7 May 1986 see page 4, line 16 - line 20 see page 6, line 5 - line 27 ---	1-20
A	FR,A,2 333 500 (ALCON LABORATORIES INC) 1 July 1977 ---	1-20
A	EP,A,0 286 791 (AMERICAN CYANAMID COMPANY) 19 October 1988 -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01565

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 21-28 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9301565
SA 71101

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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21/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9119481	26-12-91	AU-A- 8201391 EP-A- 0533836	07-01-92 31-03-93
US-A-3920810	18-11-75	None	
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82